105 Rec'd PCT/PTO 26 MAR 1997

FORM PTO-1390 (REV 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 2121-128PCT

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): New 08/809650

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR95/01239	26 September 1995	26 September 1994

TITLE OF INVENTION
COMPOSITIONS OF MURAMYL PEPTIDES INHABITING THE REPLICATION OF HIV

APPLICANT(S) FOR DO/EO/US
BAHG, Georges

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

1.) International Search Report (PCT/ISA/210)
2.) Zero (0) Sheet of Formal Drawings

U.S. APPLICATION NO (if known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
New	PCT/FR95/01239	2121-128PCT

	CALCULATIONS PTO USE ONLY
17. ☐ The following fees are submitted:	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
Search Report has been prepared by the EPO or JPO **$910.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$700.00**	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$770.00**	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$1040.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$96.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 910.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	24	- 20 =	4	X $22.00	$ 88.00
Independent claims	1	- 3 =		X $80.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	Yes			+ $260.00	$ 260.00
TOTAL OF ABOVE CALCULATIONS =					$ 1388.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$
SUBTOTAL =					$ 1388.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$
TOTAL NATIONAL FEE =					$ 1388.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$
TOTAL FEES ENCLOSED =					$ 1388.00
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 1388.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448 . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P. O. Box 747
Falls Church, VA 22040 - 0747

SIGNATURE:

SVENSSON, Leonard R.
NAME

30,330
REGISTRATION NUMBER

March 26, 1997

/sas

PATENT
2121-128PCT

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Georges BAHR

Serial No.: New Group:

Int'l. PCT No. PCT FR95/01239 Examiner:

Filed: March 26, 1997

For: COMPOSITIONS OF MURAMYL PEPTIDES INHIBITING THE REPLICATION OF HIV

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

March 26, 1997

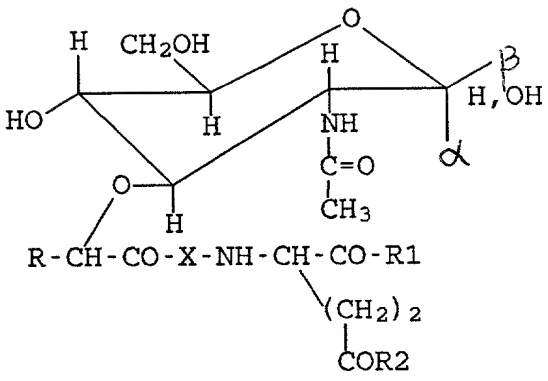
Sir:

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

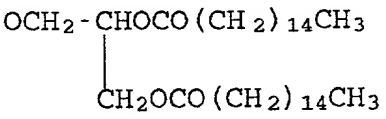
IN THE CLAIMS:

Please cancel claims 1-13 and substitute the following claims therefor:

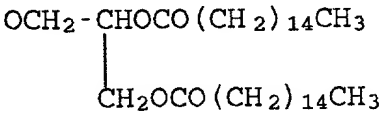
--14. A process for inhibiting the replication of acquired immunodeficiency retroviruses in man or in those mammals which they are capable of infecting, which comprises administering to them an effective amount of a muramyl peptide of formula:



in which the group R is a hydrogen or a methyl group; X is an L-alanyl, L-threonyl or L-lysyl residue, and R1 is a hydroxyl, an amino or an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, R2 is, independently of R1, a hydroxyl, an amino or an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, or a group:



it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is an $O(CH_2)_xH$ group as defined above, and that R2 cannot be a group:



--.

--15. The process of claim 14, wherein the muramyl peptide has the above-mentioned general formula in which the R group is a hydrogen or a methyl group; X is an L-alanyl or L-threonyl residue, and R1 and R2 are, independently of each other, hydroxyl, amino or $O(CH_2)_xH$ groups with x=1, 2, 3 or 4, it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is an $O(CH_2)_xH$ group as defined above.--

--16. The process of claim 14, wherein said effective amount of the muramyl peptide is an amount capable of causing a 100% inhibition of the replication of retroviruses in primary cultures of monocytes of the host.--

--17. The process of claim 14, wherein the muramyl peptide has the formula of claim 1, in which:

- the group R is a methyl group, and
- the group R2 is an NH_2 group.--

--18. The process of claim 17, wherein the muramyl peptide is Murametide.--

--19. The process of claim 18, wherein the muramyl peptide is Murabutide.--

--20. The process of claim 14, which is for the prevention or treatment of AIDS or related syndromes, especially Kaposi's sarcoma.--

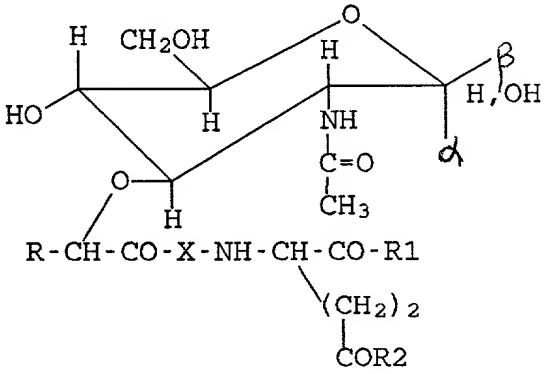
--21. The process of claim 14, which comprises administering said muramyl peptide together with another molecule capable of enhancing the anti-retroviral action of said muramyl peptide.--

--22. The process of claim 21, wherein the other molecule is a cytokine, such as an α-, β- or γ- interferon.--

--23. The process of claim 21, wherein the other molecule is GM-CSF.--

--24. The process of claim 21, wherein the other molecule is a protease inhibitor.--

--25. The process of claim 14, wherein the muramyl peptide has the formula:



in which the group R is a methyl group; X is an L-alanyl residue, and R1 is an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, R2 is, independently of R1, either an amino or an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, and wherein said effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retrovirus in primary cultures of monocytes of the host.--

--26. The process of claim 25, wherein both R1 and R2 are $O(CH_2)_xH$ groups.--

--27. The process of claim 25, wherein the muramyl peptide is Murametide.--

--28. The process of claim 25, wherein the muramyl peptide is Murabutide.--

--29. The process of claim 25, which is for the prevention or treatment of AIDS or related syndromes, especially Kaposi's sarcoma.--

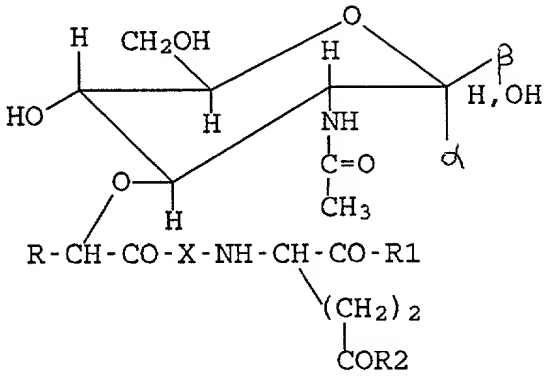
--30. The process of claim 25, which comprises administering said muramyl peptide together with another molecule capable of enhancing the anti-retroviral action of said muramyl peptide.--

--31. The process of claim 30, wherein the other molecule is a cytokine, such as an α-, β- or γ- interferon.--

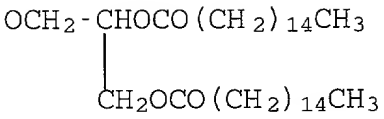
--32. The process of claim 30, wherein the other molecule is GM-CSF.--

--33. The process of claim 30, wherein the other molecule is a protease inhibitor.--

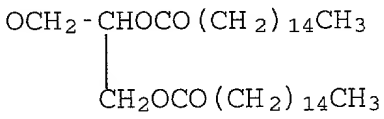
--34. The process of claim 14, wherein the muramyl peptide has the formula:



in which the group R is a methyl group; X is an L-alanyl or L-threonyl residue, and R1 is an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, R2 is, independently of R1, an amino or an $O(CH_2)_xH$ group with x=1, 2, 3 or 4, or a group:



it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is an $O(CH_2)_xH$ group as defined above, and that R2 cannot be a group:



and wherein said effective amount is also an amount that is capable of causing a 100% inhibition of the replication of said retrovirus in primary cultures of monocytes of the host.--

REMARKS

Claims 1-13 have been deleted, and claims 14-34 have been added in order to better define Applicant's invention.

Favorable action on the above-identified application is respectfully requested.

Please charge any fees or credit any overpayment pursuant to 37 CFR 1.16 or 1.17 to Deposit Account No. 02-2448.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: _____

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2121-128PCT

COMPOSITIONS OF MURAMYL PEPTIDES INHIBITING THE REPLICATION OF HIV

Acquired immunodeficiency syndrome (AIDS) is a devastating disease caused by infection by the HIV retrovirus. A lot of effort has been devoted to finding medicaments capable of inhibiting the replication of the virus. However, few significant successes have been obtained so far. Although HIV can infect many different cells, the disease is predominantly caused by the destruction and/or the dysfunction of a subpopulation of lymphocytes called helper T cells. The persistence of the infection by the virus has not long ago been attributed to its capacity to infect another major cell population, the monocyte/macrophage line, which is thought to serve as a reservoir for a continuous release of the virus. The major role played by this HIV line in the persistence and the progression of the disease has been explained by 1) the isolation of monocytotropic variants of HIV from the circulating blood leukocytes and tissue macrophages of infected subjects at all stages of the infection (J. Virology, ; Vol. 65, pages 356-363, 1991) and, 2) the direct correlation between an absence of systemic immunity dysfunction in the infected host and an absence of viral replication in the monocyte/macrophage line (J. infectious diseases, Vol. 168, pages 1140-1147, 1993). Furthermore, the inhibition of a virus-producing

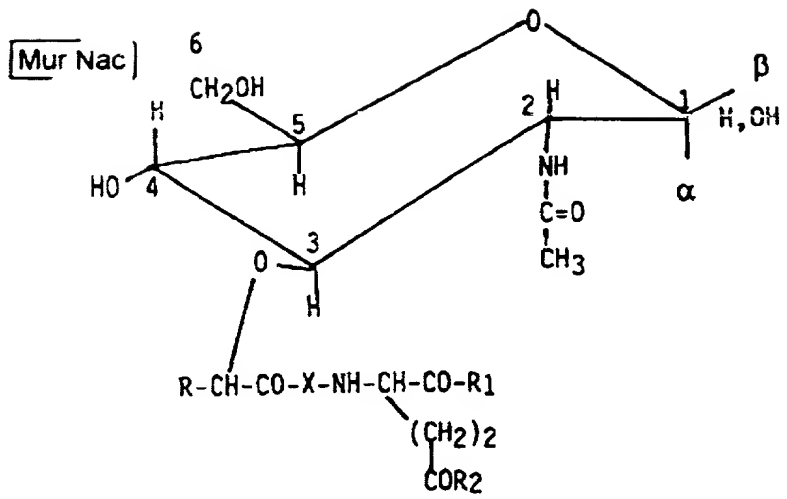
infection in the monocytes appears to be linked to a large extent to the inhibition of the monocytic proliferation, which suggests that the replication of the virus depends on a preliminary obligatory stage of high proliferation of the monocytic cell. Thus, the proliferation of this population is thought to be an obligatory passage for the manifestation of the infectious HIV character. Thus, the hypothesis has been formulated that substances capable of inhibiting monocytic replication might also inhibit the replication of HIV (J. Clinical Investigation, Vol. 89, pages 1154-1160, 1992).

Muramyl peptides are synthetic copies of the bacterial wall and have been found to be capable of highly numerous immunopharmacological activities on the monocyte/macrophage line (Federation proceedings, Vol. 45, pages 2541-2544, 1986). Furthermore, the initial molecule N-acetyl-muramyl-L-alanyl-D-Isoglutamine (Nac-Mur-L-Ala-DisoGln) also called Muramyl dipeptide or MDP, has been described to be capable of inhibiting the proliferation of guinea pig macrophages (Cellular Immunology, Vol. 89, pages 427-438, 1984). In another study using established lymphocyte cell lines or established lines of monocyte-type cells, MDP was found to be endowed with the capacity of partially inhibiting the replication of HIV when it is used in vitro at very high doses of 1000 µg/ml (AIDS Research and Human Retroviruses, Vol 6, pages 393/394, 1990). However, besides the fact that the use of MDP in human clinical medicine is difficult to envisage because of the side effects which it induces, the observed effects, even at these high doses in the experimental system used, would not presage any therapeutic efficacy towards HIV infection. Lazdins et al (AIDS Research and Human Retroviruses, Vol. 6, pages 1157-1161, 1990) have shown, in vitro, similar properties of inhibition of the replication of HIV for a muramyl peptide having a better therapeutic index than MDP : MTP-PE. This molecule, in free form, was added repeatedly, before

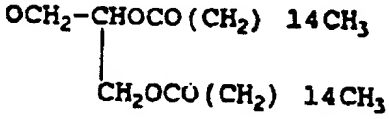
and after HIV infection, to cultures of macrophages derived from cultured human monocytes. However, it was able to induce, under these conditions, only a partial reduction in viral replication. It should be emphasized that MTP-PE was not capable, either in the free form or incorporated into liposomes, of causing total suppression of viral replication. In addition, its activity can be exerted only if this component is present on the day the cell culture is infected by the virus. If the compound is added a day before or 4 days after the culture, its activity is minimal.

These results only make more surprising those which have been obtained with another category of muramyl peptides, which have been found to allow complete inhibition of the proliferation of HIV, especially in primary cultures of moncytes, and this at much lower doses. Their lower toxicity coming on top of these favorable effects, therefore make them suitable for the preparation of medicaments capable of preventing or treating AIDS and/or of the related syndromes.

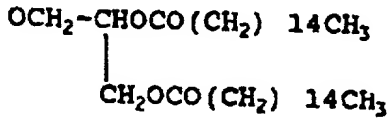
The invention relates more particularly to the use, for the preparation of medicaments inhibiting the replication of acquired immunodeficiency retroviruses in man or those of mammals which they are capable of infecting, of a muramyl peptide of formula:



in which the group R is a hydrogen or a methyl group; X is an L-alanyl, L-threonyl or L-lysyl residue, and R1 is a hydroxyl, an amino or an $O(CH2)_xH$ group with x=1,2,3 or 4, R2 is, independently of R1, a hydroxyl, an amino or an $O(CH_2)_xH$ group with x=1,2,3 or 4, or a group



it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is still an $O(CH2)_xH$ group as defined above, and that R2 cannot be:
a group

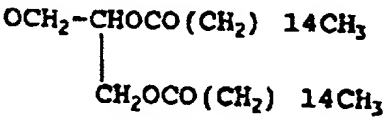


A subcategory of muramyl peptides preferred for the production of the abovementioned medicaments consists of hydrophilic muramyl peptides corresponding to the abovementioned general formula in which the R group is a hydrogen or a methyl group; X is an L-alanyl or L-threonyl residue, and R1 and R2 are, independently of each other, hydroxyl, amino or $O(CH2)_xH$ groups with x=1,2,3 or 4, it being understood that, when X is an

L-alanyl residue, at least one of these two groups R1 and R2 is still an $O(CH2)_xH$ group as defined above.

Preferred compounds for use according to the invention are Murabutide (Nac-Mur-L-Ala-DGln $O_nC_4H_9$) and Murametide (Nac-Mur-L-Ala-DGln OMe). These molecules exhibit an excellent activity profile in man; they are free of side effects and have demonstrated their very good tolerance, during clinical trials carried out in healthy volunteers and in cancer subjects.

Another preferred subcategory is that corresponding to the abovementioned general formula and in which R2 is a group



for example one of the following two compounds:

- Nac-Mur-L-Lys D-iso-Gln-glycerol, sn dipalmitoyl, and
- Nac-Mur-L-Thr D-isoGln-glycerol sn dipalmitoyl.

It is in this regard remarkable that the abovementioned muramyl peptides are capable, at relatively low concentrations, of exerting a complete inhibition, up to 100%, of the proliferation of HIV, in primary cultures of monocytes, and this more particularly in the experimental procedures which will be referred to hereinafter.

It is particularly important to note that the manifestation of the inhibitory effect of these muramyl peptides towards retroviral replication is not linked to a simultaneity of infection of the monocytes and of treatment of the latter with these muramyl peptides.

Additional characteristics of the invention will appear further in [lacuna]

Additional characteristics of the invention will appear further in the description which follows, of the biological effects exerted by two preferred muramyl peptides towards the replication of HIV in primary cultures of human monocytes collected from healthy volunteers.

In example 1, Murabutide and Murametide demonstrated their capacity to inhibit the proliferation of macrophages in culture. For that, monocytes collected from a donor are cultured for 5 days either a) without stimulation (so as to evaluate their spontaneous proliferation level) or b) in the presence of human recombinant interleukin-3 (hr IL-3) or c) in the presence of both hr IL-3 and hr GM-CSF human recombinant "granulocyte-macrophage colony stimulating factor". These two treatments make it possible to obtain a high level of proliferation. The compounds of the invention are added to the culture medium a day before the addition of tritiated thymidine (^{3}H-thymidine). The dividing cells incorporate this thymidine. The cells (which have differentiated into macrophages during the duration of the culture) are recovered and washed, and the proliferation level is evaluated by measuring, in a beta counter, the quantity of ^{3}H incorporated according to conventional methods as described in Blood, Vol. 76, pages 1490-1493, 1990. The results are presented in Table 1 and show that the two derivatives are capable, even at the dose of 1 µg/ml, of inhibiting the proliferation of macrophages stimulated with IL-$_3$ or the combination IL-$_3$/GM-CSF. The effect of inhibition of spontaneous proliferation was observed with 10 µg/ml of Murabutide and 10 or 50 µg/ml of Murametide.

Example 2 demonstrates the effect of Murabutide and Murametide on the level of replication of HIV in primary cultures of human monocytes collected from healthy volunteers. Monocyte cultures were infected on day 0 with an HIV source (HTLV III Ba-L) which exhibits a tropism for the monocytes. Some cultures were treated with different concentrations of the compounds either 1 day before, or the same day, or 1 day after inoculation with HIV. The replication of the virus was evaluated on day 7 by measurement of the quantity of viral protein P24 in the supernatants as described in Blood, Vol. 76,

page 1490-1493, 1990. The results presented in Table 2 show clearly that the treatment with Murabutide at a concentration of 10 to 50 µg/ml completely inhibits viral replication whether the treatment has been performed on day -1, on day 0 or on day +1 in relation to the infection. Similarly, the treatment with Murametide made it possible to observe a highly significant suppression of viral replication and this effect is 100% at the dose of 50 µg/ml regardless, here also, of the amount of the treatment.

These results are the first described which have made it possible to obtain a complete inhibition, by a muramyl peptide, of the replication of HIV in human monocytes. It should be emphasized that the inhibition is obtained when the compound is added to the culture only once and even after infection by HIV.

The preceding data show that the muramyl peptides of the invention can be applied to the preparation of medicaments applicable to the prevention or treatment of AIDS, or related syndromes, for example Kaposi's sarcoma.

The invention is also applicable to the preparation of medicaments in which the muramyl peptides are used in combination with other therapeutic agents used to prevent or inhibit the proliferation and the diffusion of HIV in man. Among these agents, there may be mentioned the α-, β- and γ-interferons and GM-CSF.

The molecules of the invention may be used in human clinical medicine either for preventive purposes in at-risk subjects, or for curative purposes in seropositive individuals before the appearance of clinical signs or in patients having developed manifestations of AIDS. The therapeutic doses of the muramyl peptide (for example Murabutide or Murametide) to be administered either alone, or in combination with antiviral treatments, particularly cytokines, are between 1 µg and 500 µg/kg/day. The administrations may

be given by the systemic route, by subcutaneous or intravenous injection or by infusion. The treatment may consist of daily administrations or administrations at a few days' interval and may be extended by a week to several months depending on the observed effect.

In the case of seropositive or sick individuals, the treatment should be prolonged until there is no detection of antigen or of viral genes in the serum or the cells of the infected individual, respectively. In the case of at-risk individuals, the preventive treatment should be applied during the period where a risk of infection exists.

The molecules of the invention as well as the other molecules of the family of muramyl peptides may also be used as laboratory reagents so as to allow the evaluation, as anti-HIV agents, of drugs presumed to have antiviral activity. Thus suboptimal doses of muramyl peptides could be used in combination with another agent to detect a potential activity of the latter.

This type of reagent could be used in experimentation systems in vitro using monocyte/macrophage cultures as described in this patent or methods of evaluation in vivo including the use of SCID mice.

TABLE 1

Inhibition of the proliferation of primary cultures of macrophages by Murabutide or Murametide

Molecules tested (µg/ml)	Proliferation of macrophages after stimulation					
	Medium		hr IL-3		hr IL-3 + hr GM-CSF	
	Cpm*	% Inhibition	Cpm	% Inhibition	Cpm	% Inhibition
-	1500	0	3400	0	5000	0
Murabutide						
(1)	1400	7	2600	23	2100	58
(10)	100	93	600	82	1000	80
(50)	900	40	1700	50	1200	76
(100)	1500	0	2100	38	2000	60
Murametide						
(1)	300	80	1000	70	1100	78
(10)	1200	20	1700	50	1300	74
(50)	150	90	500	85	1000	80
(100)	1000	33	1600	53	1350	73

*: count per minute of ^{3}H-thymidine/culture

TABLE 2

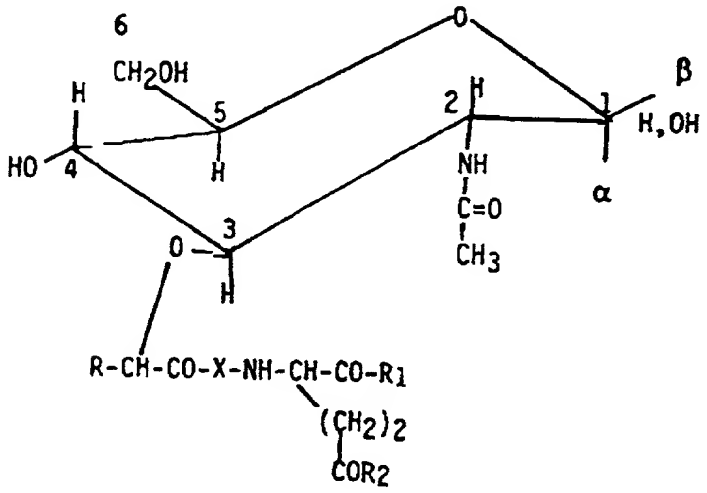
Inhibition of the replication of HIV in human monocytes by Murabutide or Murametide

Molecules tested (µg/ml)	Replication of HIV in 7- day cultures of human monocytes treated on					
	DAY -1*		DAY 0		DAY +1	
	P24 (ng/ml)	% Inhibition	P24 (ng/ml)	% Inhibition	P24 (ng/ml)	% Inhibition
Murabutide						
(0)	755	0	755	0	755	0
(1)	355	53	480	36	105	86
(10)	0	100	0	100	0	100
(50)	0	100	0	100	0	100
(100)	70	91	0	100	0	100
Murametide						
(0)	874	0	874	0	874	0
(1)	473	46	255	71	182	79
(10)	136	84	182	79	27	97
(50)	0	100	0	100	0	100
(100)	36	96	55	94	0	100

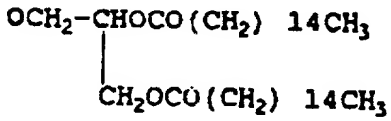
*: the day of the treatment indicates the day when the molecules were added to the culture medium compared with the day of infection with HIV which is considered as day 0.

CLAIMS

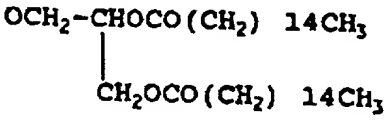
1. Use, for the preparation of medicaments inhibiting the replication of acquired immunodeficiency retroviruses in man or those in mammals which they are capable of infecting, of a muramyl peptide of formula:



in which the group R is a hydrogen or a methyl group; X is an L-alanyl, L-threonyl or L-lysyl residue, and R1 is a hydroxyl, an amino or an $O(CH2)_xH$ group with x=1,2,3 or 4, R2 is, independently of R1, a hydroxyl, an amino or an $O(CH_2)_xH$ group with x=1,2,3 or 4, or a group



it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is still an $O(CH2)_xH$ group as defined above, and that R2 cannot be:
a group



2. Use according to claim 1, of a muramyl peptide of the abovementioned general formula in which the R

group is a hydrogen or a methyl group; X is an L-alanyl or L-threonyl residue, and R1 and R2 are, independently of each other, hydroxyl, amino or $O(CH2)_xH$ groups with x=1,2,3 or 4, it being understood that, when X is an L-alanyl residue, at least one of these two groups R1 and R2 is still an $O(CH2)_xH$ group as defined above.

3. Use according to claim 1 or 2, for the preparation of medicaments inhibiting the replication of an HIV in man.

4. Use according to any one of claims 1 to 3, characterized in that the muramyl peptide is capable of inhibiting up to 100% the replication of retroviruses in primary cultures of monocytes of the host.

5. Use according to any one of claims 1 to 4, characterized in that the muramyl peptide is one of those entering into the formula of claim 1, in which

- the group R is a methyl group, and
- the group R2 is an NH_2 group.

6. Use according to claim 5, characterized in that the muramyl peptide is Murametide.

7. Use according to claim 5, characterized in that the muramyl peptide is Murabutide.

8. Use according to any one of claims 1 to 7, as reagents, for the evaluation of the efficacy of anti-retroviral medicaments, in trials in vitro or in vivo.

9. Use according to any one of claims 1 to 7, for the prevention or treatment of AIDS or related syndromes, especially Kaposi's sarcoma.

10. Use according to claim 9, for the preparation of medicaments containing, in addition to the abovementioned muramyl peptide, another molecule participating in the anti-retroviral action.

11. Use according to claim 10, characterized in that the other molecule is a cytokine, such as an a-, b- or g- interferon.

12. Use according to claim 10, characterized in that the other molecule is GM-CSF.

13. Use according to claim 10, characterized in that the other molecule is a protease inhibitor.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO.
2121-128PCT

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:*

Insert Title → COMPOSITIONS OF MURAMYL PEPTIDES INHIBITING THE REPLICATION OF HTV

Check Box If Appropriate - For Use Without Specification Attached →

the specification of which is attached hereto unless the following box is checked:

☒ The specification was filed on March 26, 1997 and was assigned United States Application No. __ or

☒ was filed as PCT International Application No. PCT/FR95/01239 and was amended under PCT Article 19 on __ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information (if appropriate) →

Prior Foreign Application(s)			Priority Claimed	
94/11460 (Number)	France (Country)	Sept. 26, 1994 (Month/Day/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Country	Application No.	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

*NOTE: Must be completed

2121-128PCT

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

RAYMOND C. STEWART (Reg. No. 21,066)
JOSEPH A. KOLASCH (Reg. No. 22,463)
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CHARLES GORENSTEIN (Reg. No. 29,271)
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JOE McKINNEY MUNCY (Reg. No. 32,334)
C. JOSEPH FARACI (Reg. No. 32,350)
TERRELL C. BIRCH (Reg. No. 19,382)
ANTHONY L. BIRCH (Reg. No. 26,122)
BERNARD L. SWEENEY (Reg. No. 24,448)
MICHAEL K. MUTTER (Reg. No. 29,680)
GERALD M. MURPHY, JR. (Reg. No. 28,977)
TERRY L. CLARK (Reg. No. 32,644)
ANDREW D. MEIKLE (Reg. No. 32,868)
ANDREW F. REISH (Reg. No. 33,443)

16

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

Send Correspondence to: **BIRCH, STEWART, KOLASCH AND BIRCH, LLP**

P.O. Box 747
Falls Church, Virginia 22040-0747
Telephone: (703) 205-8000
Facsimile: (703) 205-8050

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor: Insert Name of Inventor Insert Date This Document Is Signed Insert Residence Insert Citizenship Insert Post Office Address

GIVEN NAME: Georges | FAMILY NAME: BAHR | INVENTOR'S SIGNATURE: [signature] | DATE*: 23/4/1997
Residence (City, State & Country): Minerve 1 14 rue Paul Lafargue F-92800 PUTEAUX (France) | CITIZENSHIP: French
POST OFFICE ADDRESS (Complete Street Address including City, State & Country): Minerve 1 14 rue Paul Lafargue F-92800 PUTEAUX (France)

Full Name of Second Inventor, if any: see above

GIVEN NAME | FAMILY NAME | INVENTOR'S SIGNATURE | DATE*
Residence (City, State & Country) | CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)

Full Name of Third Inventor, if any: see above

GIVEN NAME | FAMILY NAME | INVENTOR'S SIGNATURE | DATE*
Residence (City, State & Country) | CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)

Full Name of Fourth Inventor, if any: see above

GIVEN NAME | FAMILY NAME | INVENTOR'S SIGNATURE | DATE*
Residence (City, State & Country) | CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)

Full Name of Fifth Inventor, if any: see above

GIVEN NAME | FAMILY NAME | INVENTOR'S SIGNATURE | DATE*
Residence (City, State & Country) | CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)

*Note: Must be completed — date this document is signed.

(USPTO Approved 3-90)
(Revised 8-95)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO.
2121-128PCT

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:*

Insert Title ➡ COMPOSITIONS OF MURAMYL PEPTIDES INHIBITING THE REPLICATION OF HIV

Check Box If Appropriate - For Use Without Specification Attached ➡ the specification of which is attached hereto unless the following box is checked:

[X] The specification was filed on March 26, 1997 and was assigned United States Application No. _____ or

[X] was filed as PCT International Application No PCT/FR95/01239 and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

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Insert Priority Information (if appropriate) ➡ 94/11460 (Number)	France (Country)	Sept. 26, 1994 (Month/Day/Year Filed)	[X] Yes	[ ] No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	[ ] Yes	[ ] No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	[ ] Yes	[ ] No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	[ ] Yes	[ ] No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	[ ] Yes	[ ] No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

_____ (Application Number) _____ (Filing Date)

_____ (Application Number) _____ (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Country	Application No.	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Number)	(Filing Date)	(Status — patented, pending, abandoned)

*NOTE: Must be completed.

The undersigned agree(s) to execute all papers necessary in connection with this application and any continuing, divisional or reissue applications thereof and also to execute separate assignments in connection with such applications as the Assignee may deem necessary or expedient.

The undersigned agree(s) to execute all papers necessary in connection with any interference which may be declared concerning this application or continuation, division or reissue thereof or Letter Patent(s) or reissue patent issued thereon and to cooperate with the Assignee in every way possible in obtaining and producing evidence and proceeding with such interference.

The undersigned agree(s) to execute all papers and documents and to perform any act which may be necessary in connection with claims or provisions of the International Convention for the Protection of Industrial Property or similar agreements.

The undersigned agree(s) to perform all affirmative acts which may be necessary to obtain a grant of a valid United States of America patent(s) or a grant of a valid United States of America and any foreign patent(s) to the Assignee and to vest all rights therein hereby conveyed to said Assignee as fully and entirely as the same would have been held by the undersigned if this Assignment and sale had not been made.

The undersigned hereby authorize(s) and request(s) the Patent and Trademark Office Officials in the United States of America and/or any and all foreign countries to issue any and all Letters Patents resulting from said application or any division or divisions or continuing or reissue applications thereof to the said Assignee, as Assignee of the entire interest, and hereby covenants that he has (they have) the full right to convey the entire interest herein assigned, and that he has (they have) not executed, and will not execute, any agreement in conflict herewith.

The undersigned hereby grant(s) the law firm of Birch, Stewart, Kolasch and Birch, LLP the power to insert on this Assignment any further identification which may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office for recordation of this document.

The undersigned hereby covenant(s) that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

In witness whereof, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date 25/4/1997 , Name of Inventor ✓ _____ (SEAL)
(signature) Georges BAHR

Date _____ , Name of Inventor _____ (SEAL)
(signature)

Date _____ , Name of Inventor _____ (SEAL)
(signature)

Date _____ , Name of Inventor _____ (SEAL)
(signature)

Date _____ , Name of Inventor _____ (SEAL)
(signature)

Date _____ , Name of Inventor _____ (SEAL)
(signature)

The execution by the Inventor(s) of this assignment may be witnessed by at least two other persons who sign here.

Witness _____

Witness _____